New Statistical Methods for Analyzing the National Toxicology Program's 2-year Cancer Bioassay Data

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A. Max-Iso-Poly-3 test: Modification to NTP's Poly-3 trend test

To evaluate dose-related trends in tumor incidence in 2-year rodent bioassays, the National Toxicology Program (NTP) currently uses the Poly-3 trend test (Bailer and Portier, 1987). Intrinsically, the Poly-3 trend test is the well-known Cochran-Armitage linear trend test with the modification that the sample sizes are corrected for the duration of time the tumor-free animals survived. The NTP has been using this test procedure since 1995. Although the Cochran-Armitage trend test is powerful when tumor incidences increase linearly with dose, it loses power when the incidences are not linear although monotonic in dose. Monotonic non-linear trends in tumor rates are frequently observed in 2-year NTP cancer bioassays.

Motivated by the need to improve the power of the trend test in situations where the tumor response is not linear with dose and without sacrificing power in situations where the response is linear, Peddada and Kissling (2006) introduced the Max-Iso-Poly-3 test. This test combines the Poly-3 trend test with an isotonic trend test introduced in Peddada et al. (2005). The isotonic trend test is an alternative trend test that assumes a monotonic dose-response curve without specifying the shape. The Max-Iso-Poly-3 test statistic is the maximum of the Poly-3 trend test statistic and the isotonic trend test statistic. Thus, it draws on the strengths of the Poly-3 trend test to detect linear trends and on the isotonic trend test to detect monotonic non-linear trends. Extensive simulation studies reported in Peddada and Kissling (2006) suggest that the Max-Iso-Poly-3 test enjoys very good statistical power while generally controlling the Type I error rate (i.e., false positive rate) at the nominal level.

B. Use of historical control data

There has been considerable interest among statisticians and toxicologists to develop a formal procedure for using historical control data when interpreting data from a current study. Several methods have been proposed in the literature including some Bayesian procedures. Each of these methods makes modeling assumptions that may not be realistic or appropriate for data

obtained in the NTP 2-year cancer bioassay. Hence, in the absence of an adequate formal statistical methodology, the NTP uses, informally, the range of tumor rates observed in historical controls when evaluating the significance of results obtained in a current study. Furthermore, there can be considerable subjectivity in how the historical control information is used. In 2005, the Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors recommended that a new procedure be developed for this important problem (*http://ntp.niehs.nih.gov/files/TRRSMins0905.pdf*).

Motivated by this need, Peddada et al. (2007) proposed a simple extension of the Max-Iso-Poly-3 test in which a single trend test compares the current dose groups with the historical controls as well as with the current control group. Unlike previous methods, no complicated modeling or distributional assumptions are made beyond what is assumed in the NTP's Poly-3 trend test. This trend test accounts for two sources of variation in the data, namely, variability within the current study and variability between historical studies. Extensive simulation studies suggested that this test controls the Type I error at the nominal levels and enjoys good power, especially when analyzing data on rare tumors. However, to provide more specific information about how the dose groups compare with the historical controls, we split the test into two parts, namely, (a) a test for comparing the trend in the dose groups with the historical controls, and (b) a test for comparing the current control group with the historical controls. To accomplish (a), we dropped the arm corresponding to the current control group from the trend test statistic introduced in Peddada et al. (2007). To accomplish (b), in Dinse and Peddada (2011) we introduced a test for comparing the current control group with the historical controls. Based on extensive simulation studies, we found that our test for comparing the two control groups controls the Type I error at the nominal level (Dinse and Peddada, 2011). As in Peddada et al. (2007), both tests account for the two sources of variation in the data, namely, variability within the current study and variation between historical control studies.

In conclusion, we propose that the NTP adopt three new statistical tests: (i) the Max-Iso-Poly-3 trend test, for comparing current dose groups with the current control group, (ii) the Max-Iso-Poly-3 trend test with historical controls, for comparing current dose groups with the historical controls, and (iii) a test for comparing the current controls with the historical controls. These three tests will provide three different types of information to assist toxicologists in interpreting their data.

References

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